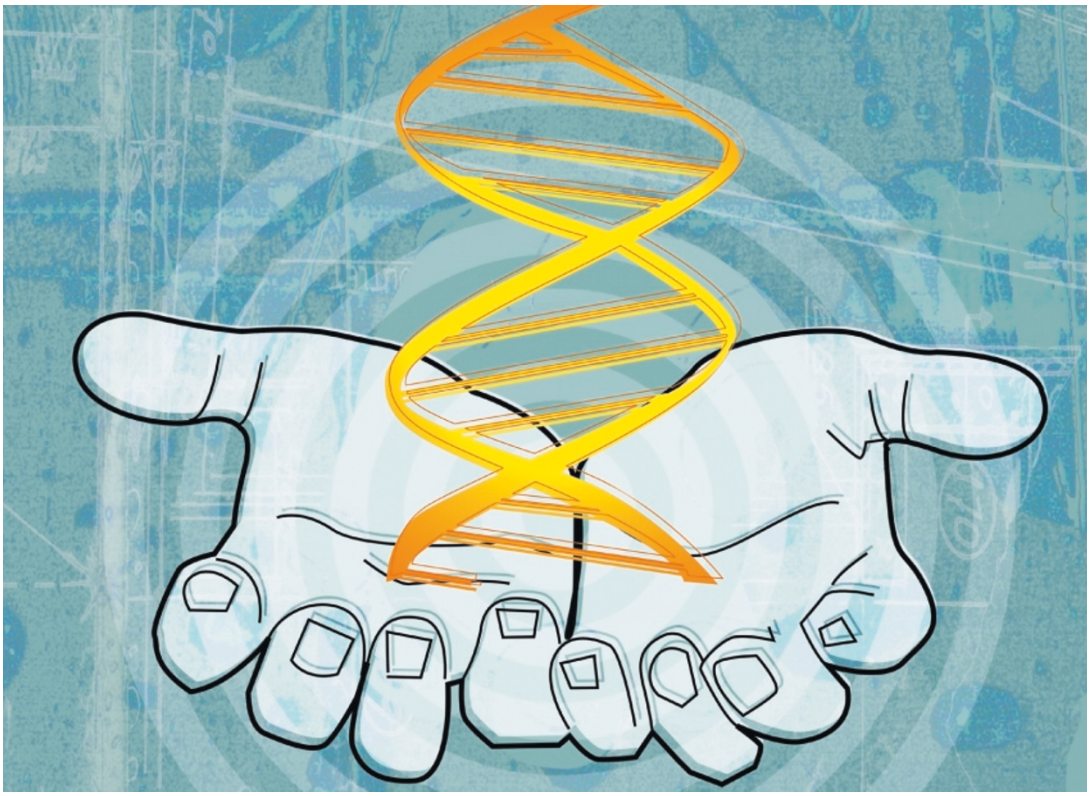

DNA REPAIR

Unpair to repair

Once they've been exposed to DNA damage, cells need to kick-start repair pathways post-haste. The ATM (ataxia-telangiectasia, mutated) kinase is known to be involved in this process — it initiates signal-transduction pathways after mammalian cells have been exposed to ionizing radiation (IR), which initiates strand breaks in DNA. Details of its exact role have been sketchy, but a report in *Nature* by Christopher Bakkenist and Michael Kastan now sheds new light on how ATM is activated.

The ATM protein belongs to the phosphoinositide 3-kinase family, but phosphorylates proteins rather than lipids. As transfected ATM is a phosphoprotein, it would make sense if its activity were modulated by post-translational modification. The authors showed that ATM is indeed phosphorylated at a specific residue, serine 1981. Experiments with antibodies that recognize Ser1981 only when it is phosphorylated (anti-1981S-P) or unphosphorylated (anti-1981S) showed that this phosphorylation occurs in response to IR. Moreover, phosphorylation of transfected kinase-inactive ATM depended on the presence of kinase-active ATM, suggesting that ATM autophosphorylates in *trans*.

What are the functional implications of this phosphorylation? The authors next did biochemical studies of ATM's domains and protein–protein interactions. They used glutathione-*S*-transferase (GST)-tagged proteins to show that the kinase and phosphorylation domains can bind to one another, and that the amino acids around Ser1981 are crucial for this interaction. This binding could theoretically occur within the same molecule (in *cis*) or between ATM molecules (in *trans*), so the authors tested whether ATM can form higher-order multimers by trying to covalently crosslink it using formaldehyde. They detected an ATM-containing complex that migrated more slowly than a denatured ATM monomer, was not seen if cells had been exposed to IR and was not recognized by the anti-1981S-P antibody.

Bakkenist and Kastan wondered whether ATM might normally exist as a higher-order complex that dissociates in response to IR through a process linked to intermolecular autophosphorylation at Ser1981. To test this, they transfected haemagglutinin (HA)-tagged ATM into 293T cells, along with wild-type-, kinase-inactive- or S1981A-Flag-tagged ATM. They then irradiated the cells and investigated which proteins bound to each other. Whereas HA-ATM could be immunoprecipitated by kinase-inactive- and S1981A-Flag-ATM after irradiation, it no longer bound wild-type-Flag-ATM. A picture emerges, then, in which ATM molecules are normally held in check in the cell by pairing up. When cells are irradiated, however, the partners phosphorylate one another and separate to repair the damaged DNA.

This model — though very elegant — doesn't address how ATM detects the damage in the first place. But Bakkenist and Kastan might have the answer. They observed that doses of radiation as low as 0.5 Gy (which initiates very few strand breaks in DNA) can trigger the autophosphorylation of a surprisingly high fraction of the cellular ATM. This, say the authors, suggests that "the introduction of DNA strand breaks must cause a change in the nucleus that can activate ATM at a distance from the break itself". In other words, ATM does not need to bind to the actual break to initiate repair. Couple this with the fact that the strand breaks caused by IR alter the topological constraints on DNA, and you have the idea that changes in the structure of chromatin might be the signal that activates ATM. In support of this, drugs that alter the chromatin structures without generating DNA strand breaks were also able to activate ATM.

Alison Mitchell

References and links

ORIGINAL RESEARCH PAPER Bakkenist, C. J. & Kastan, M. B. DNA damage activates ATM through intermolecular autophosphorylation and dimer dissociation. *Nature* **421**, 499–506 (2003)

FURTHER READING Kastan, M. B. & Lim, D.-S. The many substrates and functions of ATM. *Nature Rev. Mol. Cell Biol.* **1**, 179–186 (2000)

IN THE NEWS

Self help

As the debate surrounding the use of embryonic stem cells in therapy rages on, new findings hint that an ethically viable alternative could be to enlist our own bone marrow cells as a cellular 'repair squad'.

Reports by two independent groups, both published online in the *Proceedings of the National Academy of Sciences*, have shown that transplanted bone marrow cells can make their way to the brain and become brain cells. The findings have obvious implications for the treatment of diseases such as Parkinson's and Alzheimer's.

The discovery came from the post-mortem examination of brains from female leukaemia patients who had received bone marrow transplants from male donors after chemotherapy. Not surprisingly, blood cells in the brain originated from the bone marrow transplant, but the telltale Y chromosome of the male donors was also detected in neurons. Éva Mezey, lead researcher of the team from the US National Institute of Neurological Diseases and Stroke, said "…some kind of cell in bone marrow, most likely a stem cell, has the capacity to enter the brain and form neurons".

Helen Blau's group, based at Stanford University, believes that the cells travel the bloodstream, responding to stress and repairing damaged tissues, such as brain, muscle and possibly others, throughout the body. "The next steps are to learn which cells in the bone marrow act … how these cells are lured to tissues and how they repair damage once there.", adding, "…we may be able to direct the repair cells to where they are needed" (*Science Daily*, 4th February, 2003).

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